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REVIEW ARTICLE

The chemistry of thiohydrazonates and their utility in organic synthesis

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Syntheses, spectroscopic properties and reactions of thiohydrazonates are reviewed. The reactions of the title compounds are subdivided in sections that cover their rearrangement, oxidation and substitution. The utility of these esters in synthesis of thirty six different heterocyclic ring systems has also been presented. Their biological and industrial applications are pointed out.

Keywords: Hydrazonoyl halides; Rearrangement; Cyclization; Substitution; Heterocycles; Oxidation; Biological activity

1. Introduction and scope of the review

The thiol tautomers **1** of acid thiohydrazides are usually called hydrazonothioic acids. Functional derivatives of such acids as well as those of their oxygen analogs namely the hydrazonoic acids **2** have attracted the interest of numerous investigators throughout the world since 1950. Examples of such derivatives are hydrazonoyl halides **3**, amidrazones **4**, hydrazonates **5** and thiohydrazonates **6**. Although several review articles, covering the various aspects of hydrazonoyl halides **3** [1–6] and amidrazones **4** [7], have been reported, the chemistry of thiohydrazonate esters **6** has not been reviewed hitherto. The prodigious growth and current research interest in the chemistry of such esters during the past 35 years prompted us to write this review. For this purpose, this article covers the primary chemical literature published between 1971 and 2004 contained in *Chemical Abstracts* Chemical Substance Indexes, Volumes 74–141 inclusive. Literature prior to 1971 will not be included unless it is felt to be essential to bringing the relevant information together and to putting the problem into common perspective. In the following sections the various aspects of the chemistry of thiohydrazonates of the general formula **6**, including nomenclature, syntheses, spectroscopic properties, reactions, and more briefly, the biological activity and industrial applications of such esters, where tested, are discussed.

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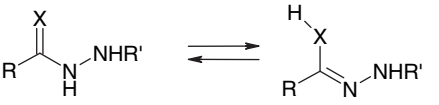
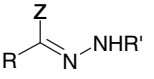


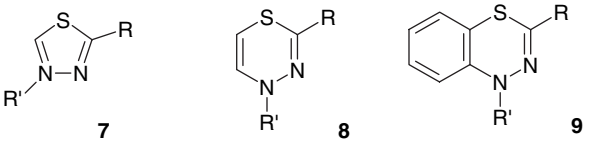
1 (2)

1, X = S; **2**, X = O



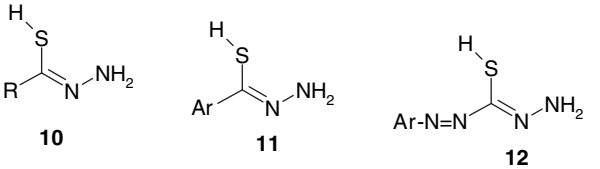
Z : **3**, Cl or Br; **4**, R'R"N; **5**, R"O; **6**, R"S

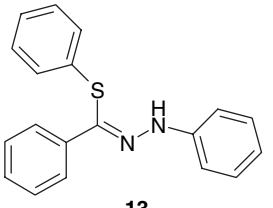
No attempt will be made in this article to list the individual thiohydrazonates described in the literature, as some of them were reported in several articles as intermediates in the reactions studied. In addition, heterocyclic compounds embracing the thiohydrazonate grouping within the ring structure such as 1,3,4-thiadiazoles **7** and 1,3,4-thiadiazines **8** as well as their benzo-derivatives **9**, will not be covered here except when these compounds arise during typical thiohydrazonate preparations.



2. Nomeclature of thiohydrazonates

Throughout this review the names of such esters are derived from either the systematic or family names of their parent acids. For example, the systemtic and (family) names of the acids **10**–**12** are alkanehydrazonothioic acid (alkanethiohydrazonic acid), arenecarbohydrazonothioic acid (arenecarbothiohydrazonic acid) and diazenecarbohydrazononothioic acid (diazenecarbothiohydrazononic acid), respectively as reported in *Chemical Abstracts* Chemical Substance Indexes. Thus, the names of the esters **13**–**15** are phenyl N-phenyl benzenecarbohydrazonothioate (or phenyl N-phenylbenzenecarbothiohydrazonate), 2-pyridyl N-phenyl-2-oxopropanehydrazonothioate (or 2-pyridyl N-phenyl-2-oxopropanethiohydrazonate) and methyl N,2-diphenyl-diazenecarbohydrazonothioate (or methyl N,2-diphenyldiazenecarbothiohydrazonate), respectively.





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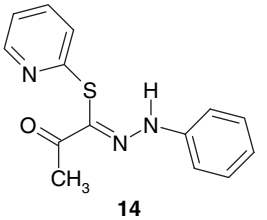

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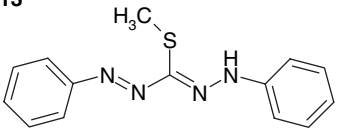

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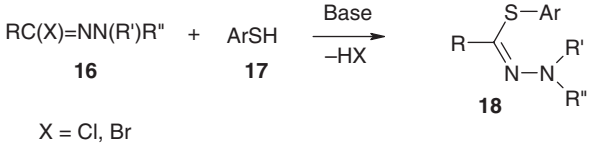
3. Synthesis of thiohydrazonates

A search of the literature has revealed much work on this subject. It is worthy to mention here that while many thiohydrazonates have been prepared, isolated and identified, some other thiohydrazonates have been identified merely as intermediates in many organic syntheses. The following are the general synthetic methods in which such esters have been isolated and identified.

3.1 *From hydrazonoyl halides*

The most widely used method for preparation of aryl thiohydrazonates **18** involves reactions of hydrazonoyl halides **16** with arenethiols **17** in the presence of a suitable base catalyst. In this method, N-aryl hydrazonoyl halides [8–23], N-heteroaryl hydrazonoyl halides [24–30] and N-methyl, N-arylhydrazonoyl halides [18] were used.



16 **17** **18**

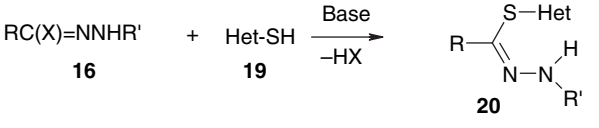
X = Cl, Br

R = Ar, EtOCO, PhNHCO, HCO, CH_3CO, PhCO, Het-CO, $ArSO_2$

R' = H, CH_3

R" = Ph, XC_6H_4 ; Heteroaryl

Similar reactions of hydrazonoyl halides **16** with heterocyclic thiols **19** in ethanol in the presence of triethylamine or sodium ethoxide afforded the corresponding thiohydrazonates **20** [15, 23, 31–41].

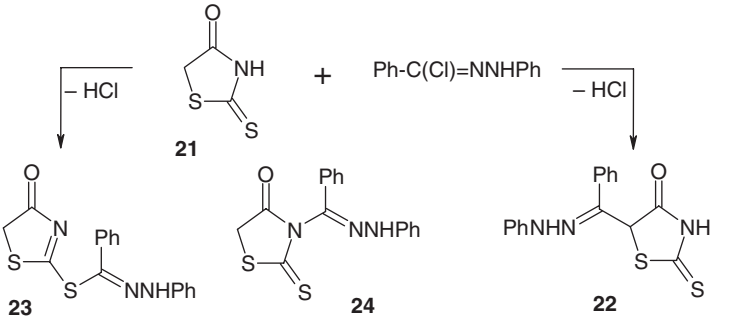


16 **19** **20**

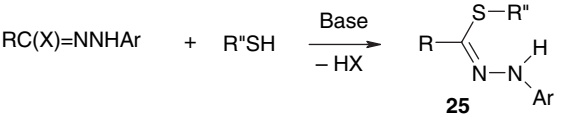
R = Ar, COOEt, PhNHCO, CH_3CO, PhCO

Het = Heteroaryl; R' = XC_6H_4

In two other reports [42, 43] it was indicated that reaction of N-phenyl benzenecarbohydrazonoyl chloride with 2-thioxothiazolin-4-one **21** in benzene in the presence of triethylamine afforded the C-substitution product **22**. No rationalization was given to account for why the expected thiohydrazonate **23** or amidrazone **24** were not formed.

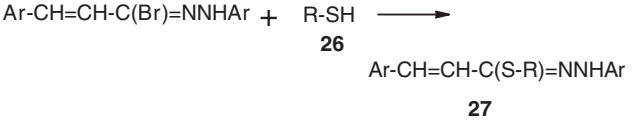


Reaction of hydrazonoyl halides with alkanethiols in ethanol in presence of sodium ethoxide yielded the respective alkyl thiohydrazonates **25** [10, 15, 44–52].



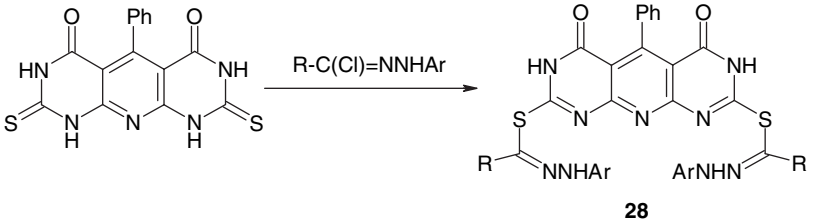
R = Ar, EtOCO, PhNHCO, CH_3CO
C-R, $-CH_2COOR$, $-CH_2$-Het, -C

Similarly, addition of 2,3,4,6-tetra-O-acetyl-D-1-thioglucopyranose **26** to selected nitrilimines, generated *in situ* from the corresponding hydrazonoyl halides, gave after deblocking the respective glucopyranosyl thiohydrazonates **27** [28, 53, 54].

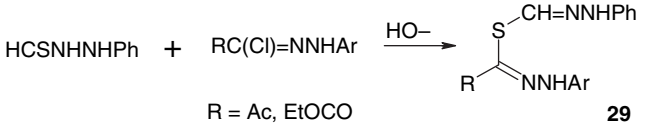


R = 1-β-D-Glucosyl, 1-β-D-Galactosyl, 1-α-D-Rhamnosyl, 1-α-D-Mannosyl

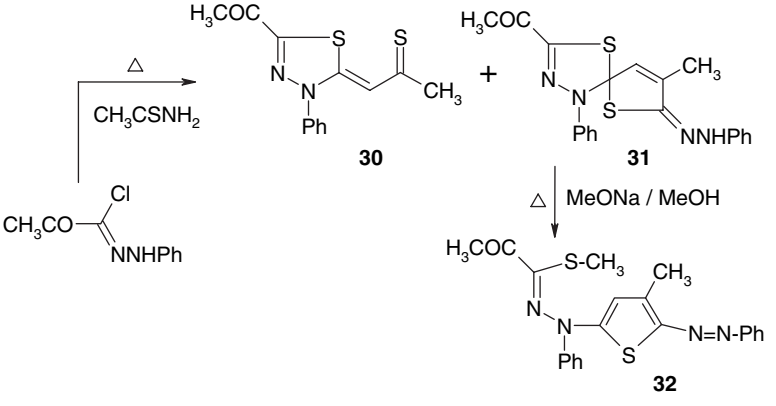
Recently, a series of the *bis*-thiohydrazonates **28** was prepared by reaction of hydrazonoyl halides with 5-phenyl-1,3,7,9-tetrahydro-2,8-dithioxopyrido[2,3-d:6,5-f']dipyrimidine-4,6(1H,9H)-dione in ethanol in the presence of sodium ethoxide [55].



Treatment of N-phenyl formicthiohydrazide with sodium hydroxide, followed by hydrazonoyl chlorides in aqueous ethanol or methanol, afforded the respective thiohydrazonates **29** [56].

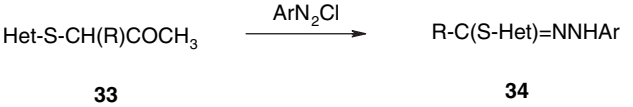


Reaction of thioacetamide with N-phenyl 2-oxopropanehydrazonoyl chloride in refluxing toluene solution was reported to give a mixture of two products namely **30** and **31** in 30 and 5% yields, respectively [57]. Treatment of **31** with methyl iodide in refluxing methanol in the presence of sodium methoxide afforded the thiohydrazonate **32** [57].



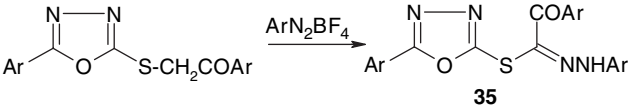
3.2 *Japp-Klingmann reaction*

The Japp-Klingmann reaction is considered the second most common method for synthesis of thiohydrazonates. Thus, coupling of diazotized aromatic amines with heteroarylthio-active methine compounds **33** in ethanol in the presence of sodium acetate gave the respective thiohydrazonates **34** [31, 32, 39, 58, 59].

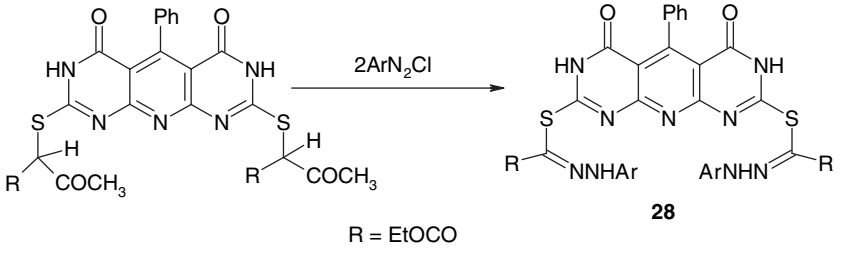


R: CH_3CO , PhCO, EtOCO, PhNHCO
Het: 4,5-diphenylimidazol-2-yl; Benzoimidazol-2-yl;
4,5-diiphenyl-1,3,4-triazol-3-yl

Also, it was reported that 5-aryl-2[(aroylmethyl)thio]-1,3,4-oxadiazoles behave as CH-acids and readily couple with aryldiazonium tetrafluoroborates at the active methylene group to give the respective thiohydrazonates **35** [60].

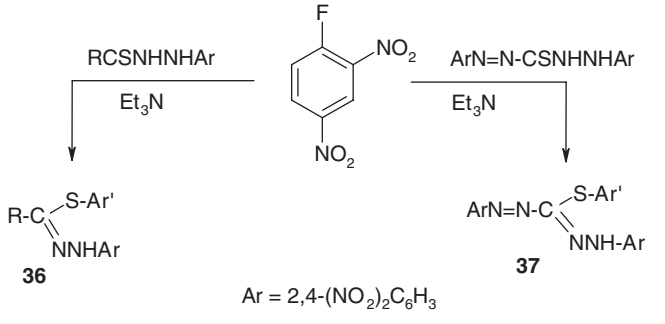


Recently, the *bis*-thiohydrazonates **28** were reported to be obtained by coupling of 2,8-di(1-ethoxycarbonyl-2-oxopropylthio)-5-phenylpyrido[2,3-d:6,5-f′]dipyrimidine-4,6 (3H,7H)-dione with diazotized anilines in ethanol in the presence of sodium acetate [55].

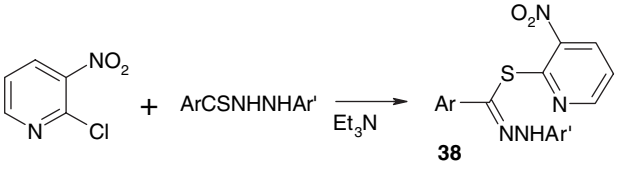


3.3 *From thiohydrazides and active halogen compounds*

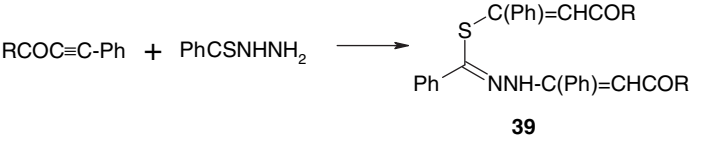
The thiohydrazonates **36** and **37** were prepared by reactions of 2,4-dinitrofluorobenzene with N-phenyl benzothiohydrazide and dithizone, respectively, in acetonitrile in presence of triethylamine [61].



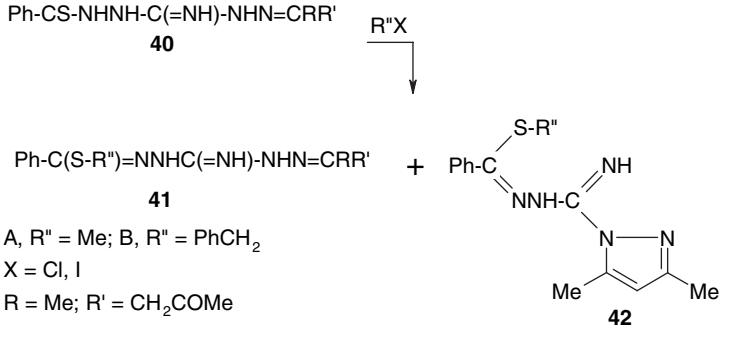
Similarly 2-chloro-3-nitropyridine was reported to react with thiohydrazides in acetonitrile in presence of triethylamine and yielded the corresponding thiohydrazonates **38** [61].



Treatment of benzoic thiohydrazide with acylacetylenes was reported to yield the thiohydrazonates **39** [62].

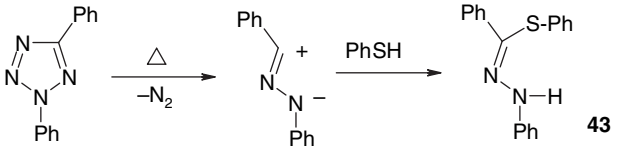


The S-methylation of the thiohydrazide **40** in alkaline media gave the thiohydrazonate **41A** and its pyrazolyl-derivative **42A**, side by side; while S-benzylation in aqueous alkali produced the ring closed product **42B** exclusively [63].



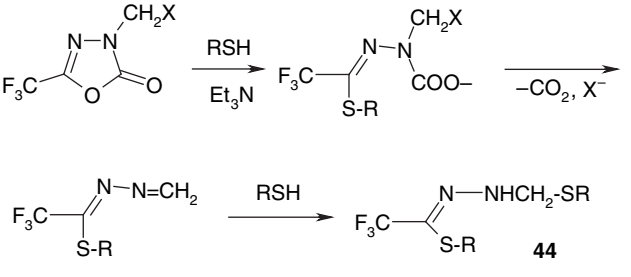
3.4 *From 2,5-diaryltetrazoles and thiophenols*

Heating 2,5-diphenyltetrazole with thiophenol was reported to give phenyl N-phenylbenzenecarbothiohydrazonate **43** *via* the 1,3-addition of thiophenol to the initially formed nitrilimine intermediate [64].



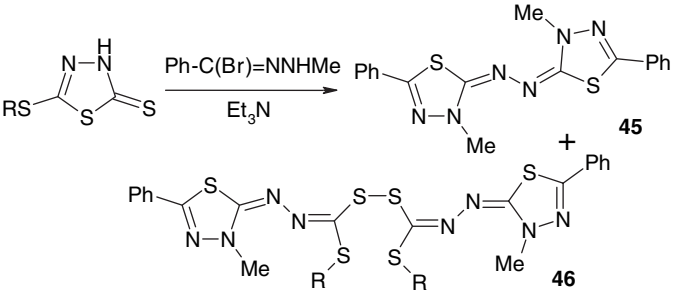
3.5 *Miscellaneous methods*

3.5.1 From 1,3,4-oxadiazol-2-ones and thiols. 3-Halomethyl-5-trifluoromethyl-1,3,4-oxadiazol-2-one gave upon heating with alkanethiols in the presence of triethylamine the respective thiohydrazonates **44** [65].



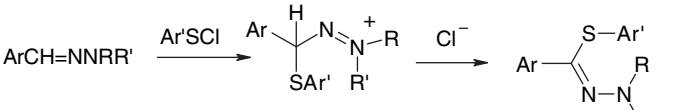
R = Me, Et, i-Pr, $PhCH_2$; X = Cl, I

3.5.2 From 1,3,4-thiadiazol-2(3H)-thiones. Reaction of N-methyl benzenecarbohydrazonoyl bromide with 5-alkylthio-1,3,4-thiadiazole-2(3H)-thiones in anhydrous tetrahydrofuran in the presence of triethylamine was reported [66] to give a mixture of 2,2′-azinobis(3-methyl-5-phenyl-2,3-dihydro-1,3,4-thiadiazole **45** and dialkyl bis(3-methyl-5-phenyl-2,3-dihydro-1,3,4-thiadiazol-2-ylidene)(thioperoxydicarbonohydrazonate) **46**.



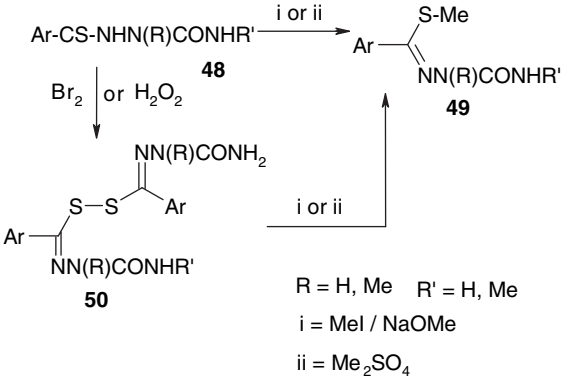
R = Et, Me, t-Bu, 4-$MeC_6H_4CH_2$, 2,4-$Cl_2C_6H_3CH_2$

3.5.3 From aldehyde hydrazones and arylsulfenyl chlorides. Reaction of N,N-disubstituted aldehyde hydrazones with 4-nitrophenylsulfenyl chloride in dichloromethane was reported to give the thiohydrazonates **47** [67].

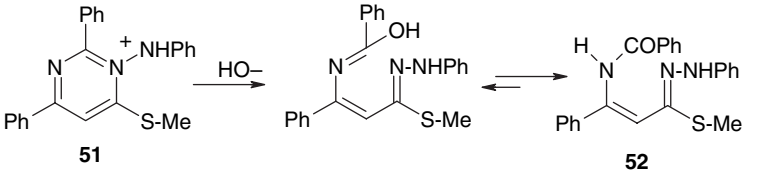


Ar' = 4-$O_2NC_6H_4$

3.5.4 Alkylation of thioaroylthiosemicarbazides. Methylation of N-thiobenzoyl-N′-substituted-semicarbazides **48** with methyl iodide in methanol in presence of sodium methoxide or with dimethyl sulfate afforded the thiohydrazonate **49** [68]. Alternatively, oxidation of **48** with bromine or hydrogen peroxide to give the disulfide **50** and treatment of the latter with methyl iodide or dimethyl sulfate under similar reaction conditions afforded the thiohydrazonates **49** [68].

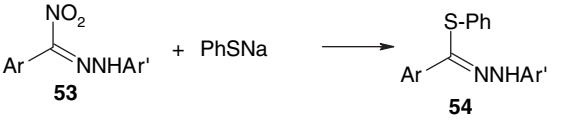


3.5.5 Alkaline hydrolysis of 4-alkylthio-3-arylaminopyrimidinium salts. Treatment of the title salts **51** with sodium hydroxide caused their hydrolysis and gave the respective thiohydrazonate **52** [69].



51 **52**

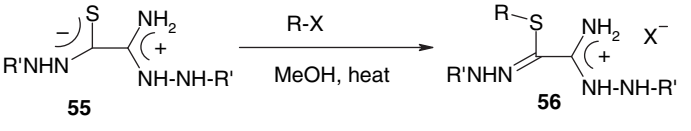
3.5.6 From α-nitrohydrazones. Treatment of N-(p-nitrophenyl) α-nitrobenzaldehyde-hydrazones **53** with sodium thiophenoxide in ethanol at room temperature was reported to give the respective phenyl benzenecarbothiohydrazonates **54** [70].



53 **54**

Ar = XC_6H_4 Ar' = $4\text{-}O_2NC_6H_4$

3.5.7 From zwitterionic thiooxalic acid derivatives. Treatment of the zwitterionic thiooxalic acid derivatives **55** in methanol with alkyl bromides or iodides yielded the respective thiohydrazonates **56** in good yields [71].

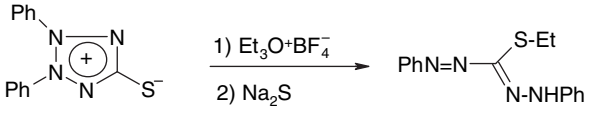


55 **56**

X = Br, I R = Me, $4\text{-}O_2NC_6H_4CH_2$, $Me(CH_2)_4$

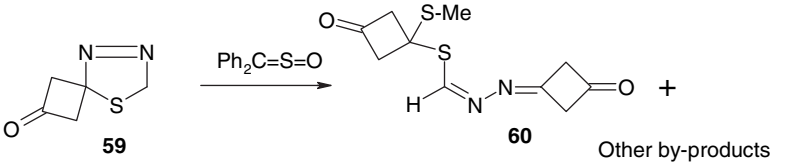
R' = H, Me, Ph

Mesoionic tetrazoles **57** reacted with Et_3O^+ BF_4^- in CH_2Cl_2 to give the corresponding tetrafluoroborates which reacted with sodium sulfide to the hydrazonothioate **58** [72].



57 **58**

Reaction of the spirocyclic-2,5-dihydro-1,3,4-thiadiazole **59** and thiobenzophenone-S-oxide in THF at 45° yielded the thiohydrazonate **60** in 23% yield in addition to other by-products [73].



59 **60** Other by-products

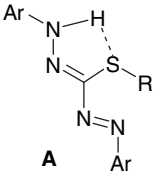
4. Spectroscopic properties of thiohydrazonates

The characteristic features of the electronic absorption spectra of several thiohydrazonates in ethanol were reported to be typical of hydrazones. For example, such esters exhibit UV maxima in the regions 360–340 and 280–270 nm [20, 21]. The logarithms of the molar extenction coefficients at the indicated wavelengths is usually higher than 4.00.

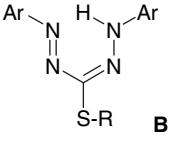
In the IR spectra, the νC=N and νNH absorption bands of thiohydrazonates appear in the regions 1615–1600 and 3350–3200 cm^{-1} [8, 17, 19, 20, 52, 55, 74, 75].

In the ^{1}H NMR spectra of thiohydrazonates, the chemical shift value of the NH proton usually is at δ 9.20–10.9 [14, 19, 23, 75, 76]. In their ^{13}C NMR spectra the chemical shift value of the imino carbon is in the region δ 120.5–136.0 [34] [65].

The mass spectra of thiohydrazonates were reported to be characterized by peaks that correspond to loss of the elements of the respective thiols from their molecular ions [8, 14, 55, 74, 77]. The results of spectroscopic studies of ^{1}H NMR, IR [78–80] and visible spectra [81], as well as flash photolysis [82] and X-ray crystallograpic analysis [83, 84] indicated that alkyl N,2-diaryldiazenecarbohydrazonothioates exist in solution as an equilibrium mixture of yellow and pink isomers. Such isomers have trans-anti-s-trans (**A**) and trans-syn-s-trans (**B**) configurations, respectively, with respect to the N=N, C=N and C−N bonds of the ester skeleton. The main feature of the yellow isomer is the presence of short NH . . . S intramolecular hydrogen bond indicating a firmly stabilized five membered ring [83, 84].



A

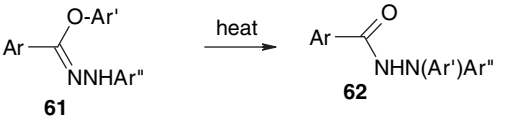


B

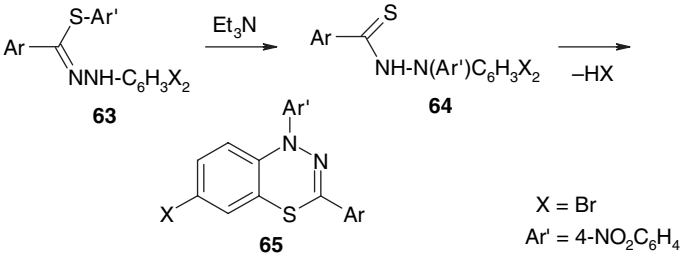
5. Chemical reactions

5.1 *Smiles rearrangement*

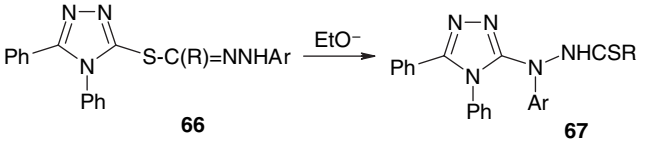
Thermolysis of hydrazonates **61** was reported to result in 1,4-rearrangement to give the respective N,N-disubstituted acid hydrazides **62** [64]. Thermal rearrangement of thiohydrazonates to the respective N′,N′-disubstituted thiohydrazides was first attempted by Hegarty *et al.* [85] but without success. Later, Elliott *et al.* [23] reported that rearrangement of thiohydrazonates can be accomplished when (i) the S-aryl is made electron deficient by substitution and/or incorporation of heteroatom(s); (ii) employing basic conditions to increase the nucleophilicity of the terminal N-atom of the hydrazonoyl system or (iii) employing acidic conditions to increase the electrophilicity of the S-aryl group if it is basic. For example, Elliott *et al.* [23] found that when the thiohydrazonates **63** were treated with triethylamine in ethanol at reflux, they yielded the respective benzo[e][1,3,4]thiadiazine derivatives **65**. The latter resulted *via* rearrangement of the thiohydrazonates and *in situ* cyclization of the resulting thiohydrazides **64**.



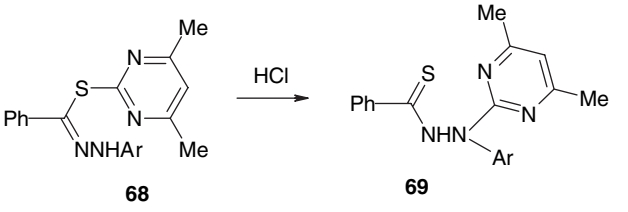
61 **62**



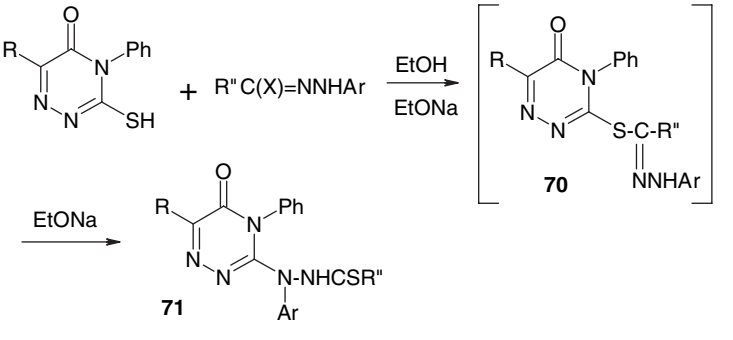
Recently Shawali *et al.* [39, 41, 86] reported that treatment of **66** with sodium ethoxide in ethanol at reflux afforded the respective thiohydrazides **67**.



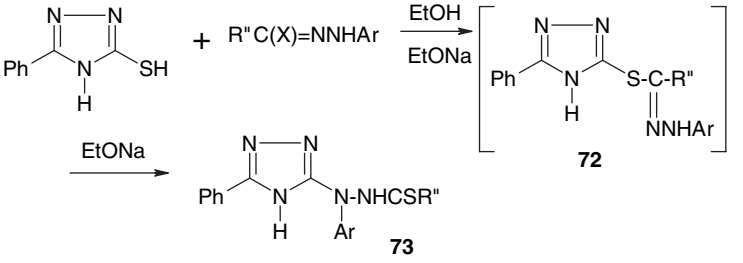
When the 2-pyrimidinyl thiohydrazonate **68** was treated with hydrochloric acid in methanol, it gave the thiohydrazide **69** in 53% yield [23].



In some cases the thiohydrazonates undergo *in situ* rearrangement during their preparation to give the respective thiohydrazides [87, 88]. For example, reactions of hydrazonoyl halides with each of 3-mercapto-4-phenyl-6-substituted-5(4H)-1,2,4-triazinone and 5-phenyl-1,3,4-triazole-3(2H)-thione in ethanol in the presence of sodium ethoxide were reported to give directly the corresponding thiohydrazides **71** and **73** *via* rearrangement of the initially formed thiohydrazonates **70** and **72**, respectively [87]. The structure of the latter thiohydrazides was confirmed by alternate synthesis [86, 88].

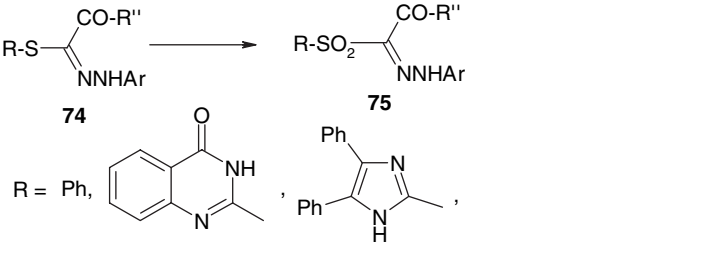


R" = Ph, EtOCO, PhNHCO, Ac, Bz



5.2 *Oxidation*

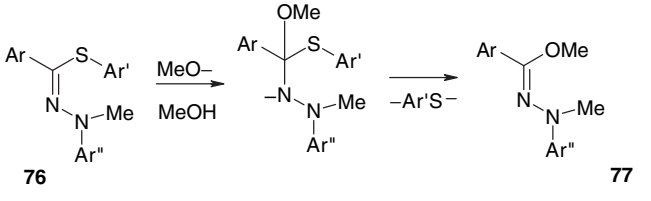
A search of literature has revealed little work on this reaction, although treatment of the thiohydrazonates **74** with hydrogen peroxide in acetic acid at room temperature was reported to give the corresponding arylhydrazonosulfone derivatives **75** [15, 89].



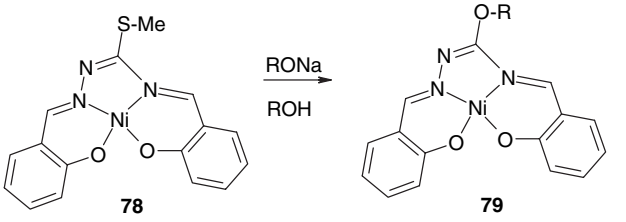
R" = EtO; Me; ArNH, 1-Naphthyl; 4-Cyano-1-*p*-tolyl-5-phenylpyrazol-3-yl

5.3 *Methanolysis*

Treatment of p-nitrophenyl N-methyl-N-2,4-dinitrophenylbenzothiohydrazonates **76** with sodium methoxide in methanol was reported to give the respective methyl N-methyl-N-2,4-dinitrophenylbenzohydrazonates **77**. A kinetic study of this reaction revealed that it proceeds *via* addition-elimination mechanism [18, 90]. Similarly, reaction of thiohydrazonate-Ni complex **78** with alcohols in presence of sodium alkaoxide was reported to the yield respective hydrazonate-Ni complexes **79** [91].



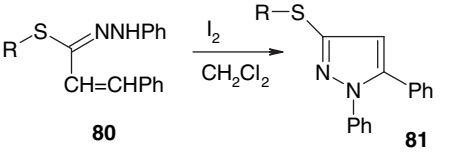
Ar' = p-$NO_2C_6H_4$ Ar" = 2,4-$(O_2N)_2C_6H_3$



R = Me, Et, Pr, Bu, Pentyl

5.4 *Synthesis of heterocycles*

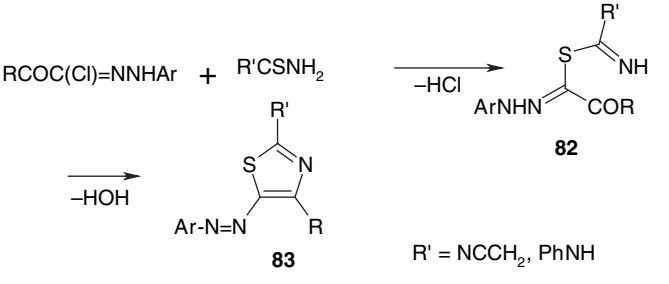
5.4.1 Pyrazoles. 1,5-Diphenylpyrazol-3-yl-2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosides **81** were easily prepared in high yields (90%) by the action of iodine or N-bromosuccinimide on the respective thiohydrazonates **80** in dichloromethane solution [54].



80 **81**

R = Protected Sugar

5.4.2 Thiazoles. Thiohydrazonates of type **82** were reported to cyclize *in situ* during their preparation from hydrazonoyl halides with thioacetamides to give 2-arylazo-3,5-disubstituted thiazoles **83** [92, 99].

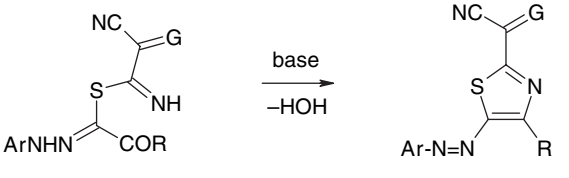


82

83

R' = $NCCH_2$, PhNH

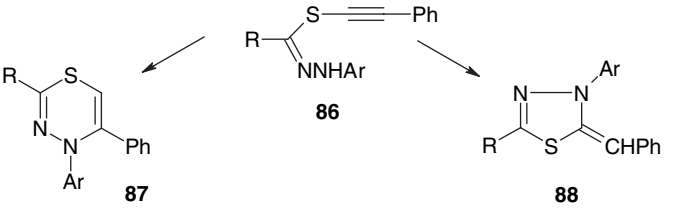
Treatment of the thiohydrazonates **84** with sodium hydroxide or triethylamine in ethanol at room temperature afforded the thiadiazole derivatives **85** together with the hydrazonoyl sulfide and malononitrile derivatives as by-products [93].



84 **85**

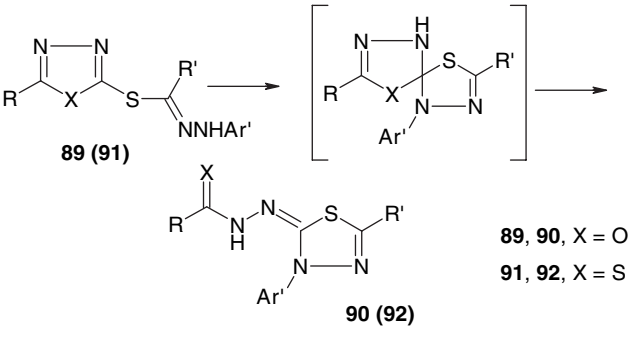
G = ArCH, ArNHN

5.4.3 1,3,4-Thiadiazolines. Alkynyl thiohydrazonates **86**, prepared by reaction of hydrazonoyl halides with potassium thioacetylenes in benzene in the presence of triethylamine, were reported to undergo cyclization to give the thiadiazine derivatives **87** in 30–100% yields [45]. In another report, it was indicated, however, that the foregoing reaction afforded the 1,3,4-thiadiazoline derivative **88** [47]. The structures of the latter were confirmed by X-ray crystallographic analyses [47].

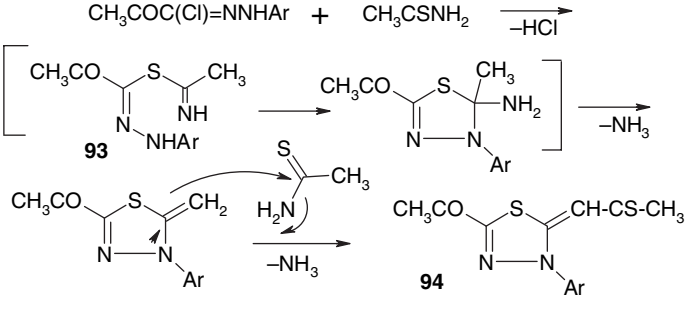


Recently, it was reported that the thiohydrazonates **89**, formed in the reaction of hydrazonoyl halides with 1,3,4-oxadiazole-2-thione in either benzene or ethanol in the presence of triethylamine at room temperature, underwent cyclization *in situ* to give the corresponding spiro compounds which displayed ring-chain tautomerism to give 3,5-diphenyl-1,3,4-thiadiazol-2(3H)-one benzoylhydrazone **90** as end products [35, 59, 94].

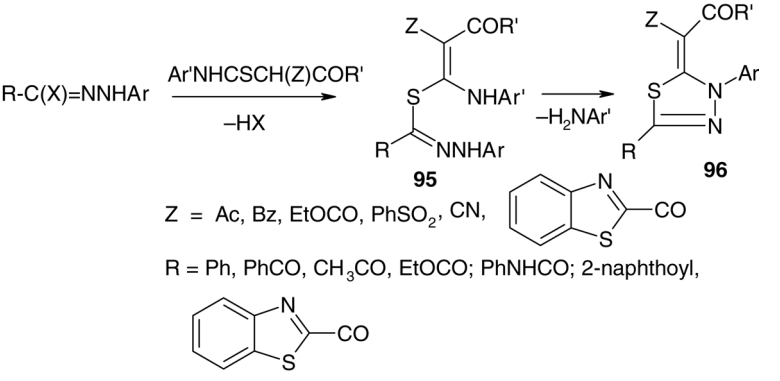
Similarly, 1,3,4-thiadiazol-2-yl thiohydrazonates **91** were reported to undergo cyclization *in situ* followed by ring-chain tautomerism, when treated with triethylamine in ethanol at room temperature, to give the isomeric thiadiazoline derivatives **92** [36].



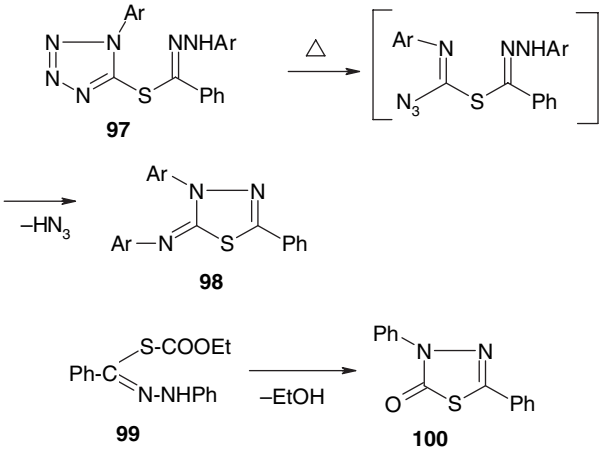
1-Iminoethyl thiohydrazonates **93**, prepared by reaction of hydrazonoyl halides with thioacetamide in refluxing toluene was reported to cyclize also *in situ* to give the 1,3,4-thidiazolone derivative **94** [57].



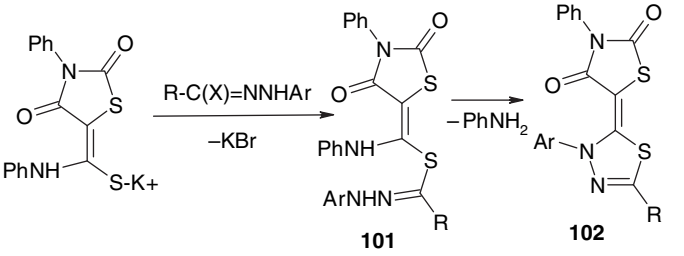
In another report 1,3,4-thiadiazoline derivatives **96** were prepared by base-catalyzed cyclization of the thiohydrazonates **95**, accessible from reaction of hydrazonoyl halides with potassium salts of the active methine thioamides [9, 95, 96].



Heating 5-tetrazolyl thiohydrazonates **97** in toluene, benzene or dimethyl sulfoxide was reported to give 2,4-diaryl-5-arylimino-1,3,4-thiadiazoles **98** [34]. Also, the thiohydrazonate **99** cyclized *in situ* during its preparation from N-phenyl benzenecarbohydrazonoyl chloride with the sodium salt of ethyl ester of monothiocarbonic acid to give 3,5-diphenyl-1,3,4-thiadiazol-2(3H)-one **100** [97].

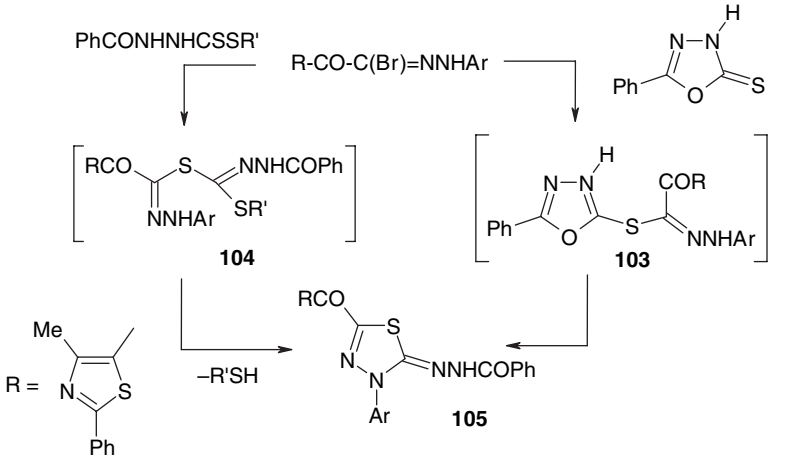


Likewise, the thiohydrazonate esters **101**, prepared from the reaction of hydrazonoyl halides with 3-phenyl-2,4-dioxotetrahydrothiazole-5-thiocarboxanilide in dimethylformamide in the presence of sodium hydroxide, was reported to cyclize *in situ* to give the thiadiazoline derivative **102** [98].

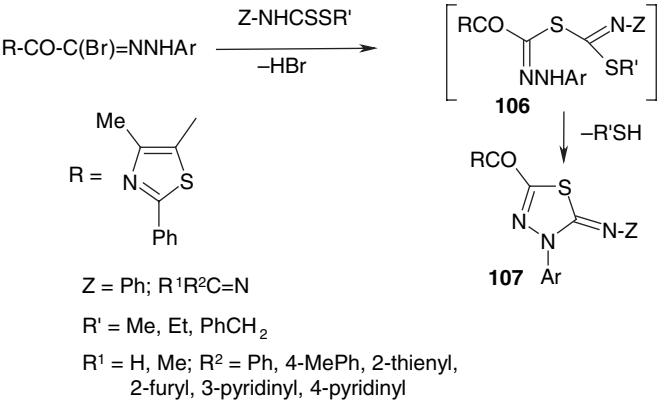


R: Ph, PhCH=CH, 2-thienyl, Ac, EtOCO, PhCO, PhNHCO, 2-thenoyl, 2-naphthoyl

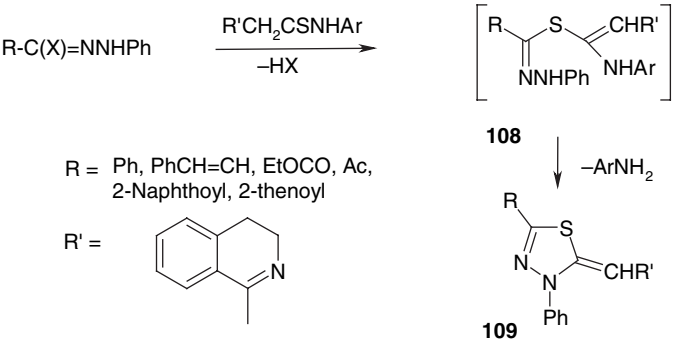
Also, 3-aryl-2-(benzoylhydrazono)-3-phenyl-5-acyl-1,3,4-thiadiazole **105** was obtained by *in situ* cyclization of the thiohydrazonate esters **103** or **104** which are formed by reaction of hydrazonoyl halides with either 5-phenyl-1,3,4-oxatriazole-2-thione or 2-benzoyl-dithiocarbazate, respectively [99, 100].



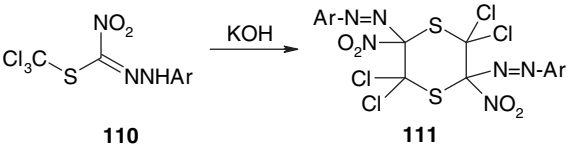
Reactions of hydrazonoyl halides with dithiocarbamate and dithiocarbazates afforded the respective 1,3,4-thiadiazole derivatives **107** *via in situ* cyclization of the initially formed thiohydrazonate esters **106** [99].



2-Substituted-1,3,4-thiadiazoline derivatives **109** were obtained by *in situ* cyclization of the thiohydrazonate **108** formed by reaction of the thioamides with hydrazonoyl halides [101, 102].



5.4.4 Dithianes. Trichloromethyl N-aryl-nitromethanehydrazonothioates **110** were cyclodimerized upon treatment with potassium hydroxide in chloroform at 0°C to give the dithianes **111** [103].

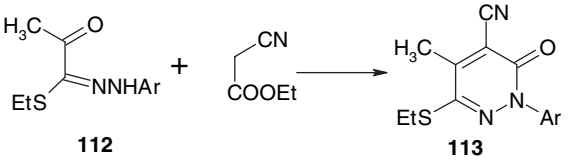


110 **111**

Ar = $RNHSO_2C_6H_4$

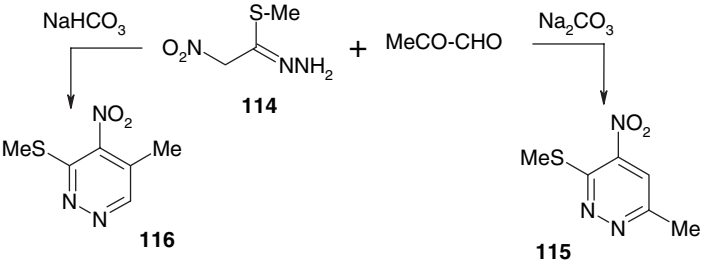
R = H, Ac, 2-thiazolyl, 4,6-dimethyl-2-pyrimidyl

5.4.5 Pyridazines. Several 2,6-diarylpyridazinone derivatives **113** were prepared by heating the thiohydrazonates **112** with ethyl cyanoacetate and ammonium acetate. Some of these derivatives were reported to exhibit immunosupressant activity with human T-lymphocytes [46, 104, 105].



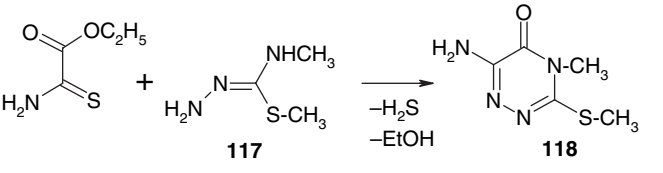
112 **113**

Reaction of thiohydrazonate **114** with methylglyoxal in ethanol in the presence of sodium carbonate was reported to give **115** whereas in the presence of sodium bicarbonate, it gave the isomeric compound **116** [106].



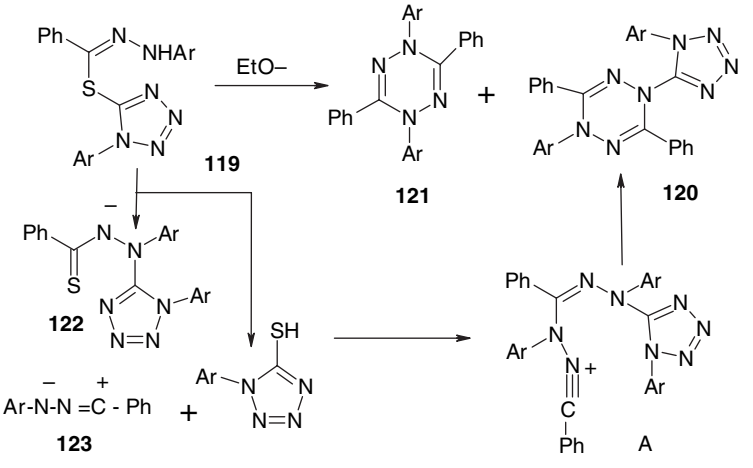
114 **116** **115**

5.4.6 1,2,4-Triazines. Reaction of ethyl thiooxoamidate with the thiohydrazonate **117** in refluxing ethanol in the presence of triethylamine afforded 6-amino-4-methyl-3-methylthio-1,2,4-triazin-5(4H)-one **118** [107].

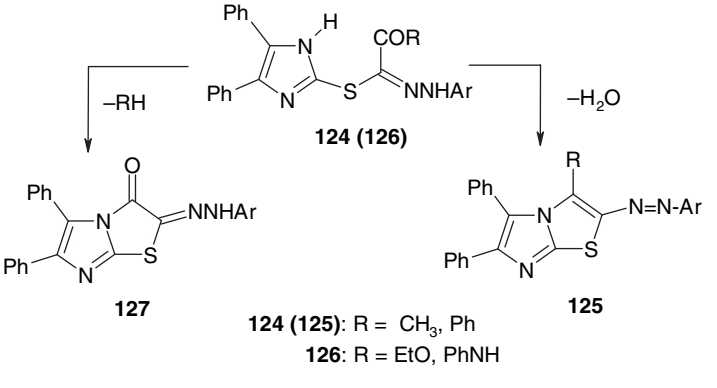


117 **118**

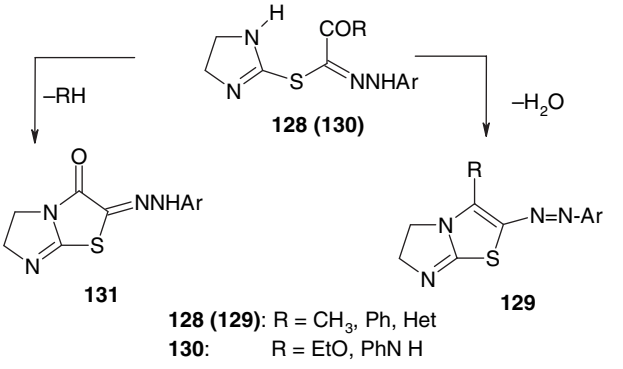
5.4.7 1,2,4.5-Tetrazines. Heating S-(1-aryl-1H-tetrazol-5-yl)benzothiohydrazonates **119** with sodium ethoxide in ethanol under reflux for 5 minutes, was reported to yield the substituted dihydrotetrazines **120** in good yields [37]. In all cases examined, the symmetrical tetrazines **121** were formed as minor products, which are likely to result from dimerization of the nitrilimines. It was indicated that the steps leading to the unsymmetrical tetrazines **120** are obscure and they must involve an interaction between **122** and **123** which results in desulfurization and loss of an aryl group possibly involving a species such as **A**.



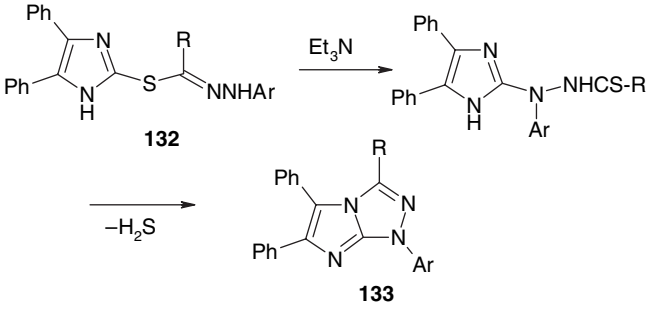
5.4.8 Imidazo[2,1-*b*]thiazoles. Imidazo[2,1-*b*]thiazoles **125** were prepared by cyclization of 2-imidazolylthio hydrazonates **124**, derived from α-oxoalkanehydrazonoyl halides and 2-imidazolethiol [15, 31, 32]. Refluxing the thiohydrazonates **126** in ethanol containing triethylamine afforded 5,6-diphenyl-2-phenylhydrazonoimidazo[2,1-b]thiazol-3-one **127** [32].



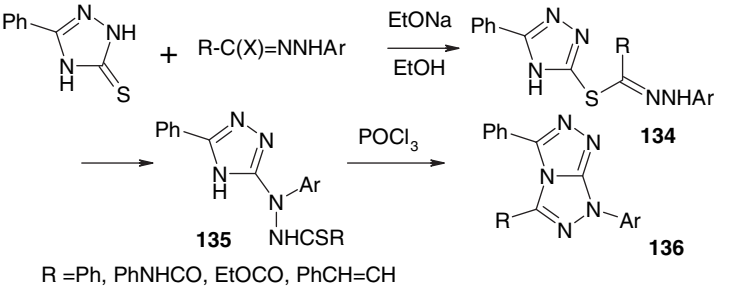
Similarly, the thiohydrazonates **128** and **130**, derived from α-ketohydrazonoyl halides and 4,5-dihydroimidazole-2-thiol, cyclized upon refluxing in ethanol in the presence of triethylamine to furnish the imidazo[2,1-*b*]thiazole derivatives **129** and **131**, respectively [11, 33].



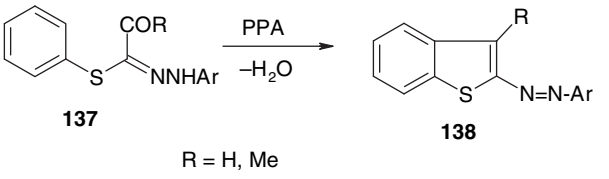
5.4.9 Imidazo[2,1-*c*]-1,2,4-triazoles. Thiohydrazonates **132** derived from reaction of hydrazonoyl halides with 4,5-diphenyl-2-imidazolethiol yielded the title ring system **133** upon treatment with triethylamine [108].



5.4.10 1,2,4-Triazolo[3,4-*c*]-1,2,4-triazoles. Reaction of hydrazonoyl chloride with 3-phenyl-1,2,4-triazole-5-thione in ethanol in the presence of sodium ethoxide at room temperature was reported to give the thiohydrazide **135** as end product *via* rearrangement of the initially formed thiohydrazonate **134**. Refluxing the latter with phosphoryl chloride [86] or in pyridine [88] afforded the respective 1,3,5-trisubstituted-1,2,4-triazolo[3,4-*c*]-1,2,4-triazoles **136**. The structure of the latter products were confirmed by their alternate synthesis via reaction of hydrazonoyl halides with 5-phenyl-3-methylthio-1,2,4-riazole in refluxing ethanol in the presence of sodium ethoxide [88].



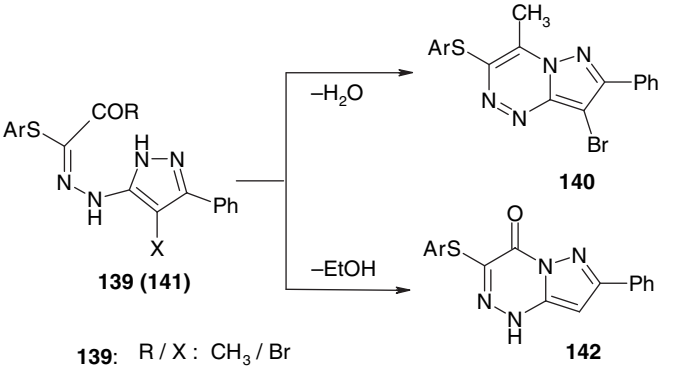
5.4.11 Thianaphthenes. 2-Arylazo-3-substituted-thionaphthenes **138** were prepared by cyclizing the thiohydrazonates **137** with polyphosphoric acid [76].



137 **138**

R = H, Me

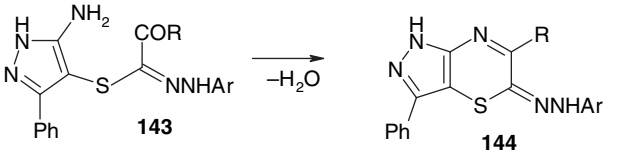
5.4.12 Pyrazolo[5,1-*c*][1,2,4]triazines. Thiohydrazonates **139** and **141**, prepared from sodium thiophenolate and the respective hydrazonoyl chlorides, were reported to cyclize *in situ* to give the respective pyrazolo[1,5-*c*][1,2,4]triazine derivatives **140** and **142**, respectively [109, 110].



139 (141) **140** **142**

139: R / X : CH_3 / Br
141: R / X : EtO / H

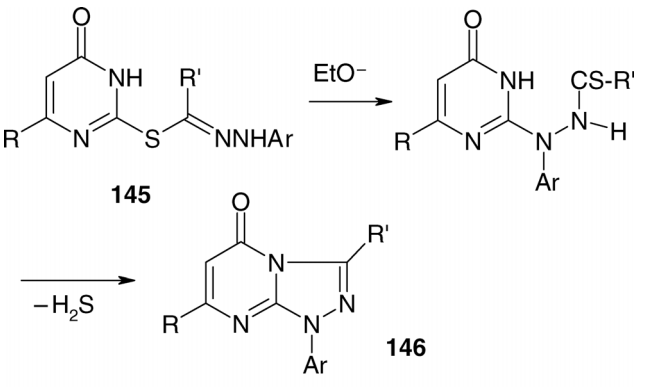
5.4.13 Pyrazolo[4,3-*b*]-1,4-thiazines. Cyclization of (5-amino-3-phenylpyrazol-4-yl) thiohydrazonate **143** in refluxing ethanol furnished the pyrazolo[4,3-*b*]thiazine derivatives **144** [33].



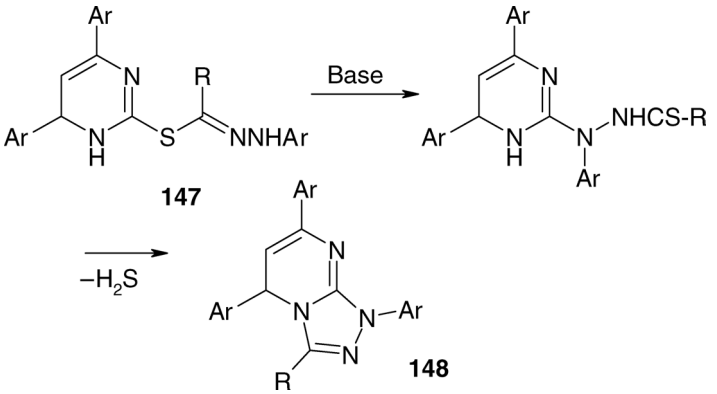
143 **144**

R: Me , Ph

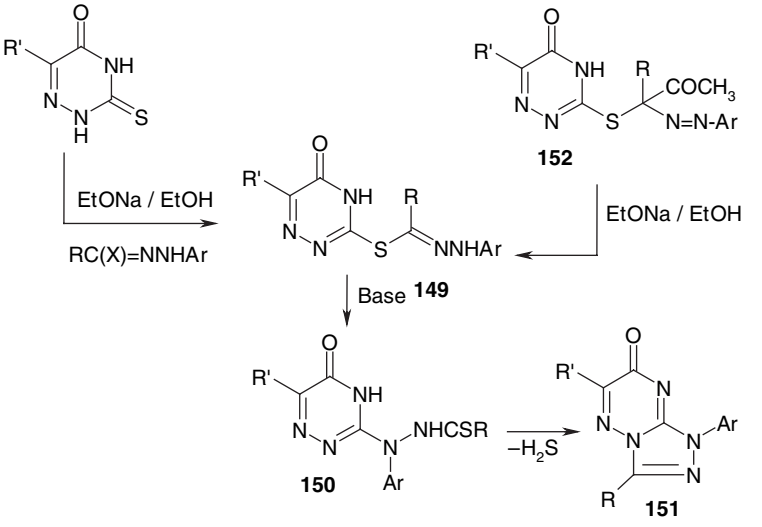
5.4.14 1,2,4-Triazolo[4,3-*a*]pyrimidines. Various derivatives of this ring system **146** were prepared by treatment of S-(6-substituted-4-oxo-3H-pyrimidin-2-yl) thiohydrazonates **145** with sodium ethoxide in ethanol under reflux [111–115].



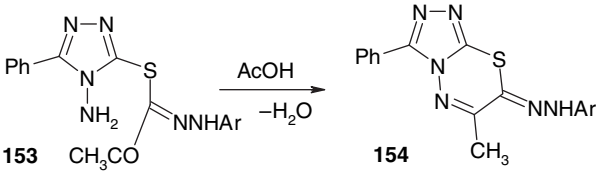
Similarly, treatment of the thiohydrazonate **147** with a base resulted in its rearrangement and cyclization of the respective thiohydrazide to give 1H,5H-1,2,4-triazolo[4,3-*a*]pyrimidines **148** [116].



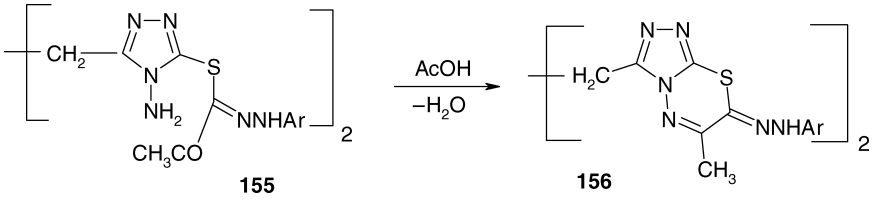
5.4.15 1,2,4-Triazolo[4,3-*b*]-1,2,4-triazines. Recently the synthesis of various derivatives of this ring system was achieved by reacting the respective hydrazonoyl halides with 1,2,4-triazine-2-thiones [38, 41]. It was suggested that the initially formed thiohydrazonates **149** underwent Smiles rearrangement to give the thiohydrazides **150** which in turn cyclized *via* elimination of hydrogen sulfide to yield the respective 1,2,4-triazolo[4,3-*b*]-1,2,4-triazine derivatives **151** as end products [38, 41]. The involvement of the thiohydrazonate **149** as a possible intermediate in synthesis was evidenced by an alternate synthesis of **151**. Thus, treatment of the the azo derivatives **152** with sodium ethoxide in ethanol yielded the respective 1,2,4-triazolo[4,3-*b*]-1,2,4-triazin-7(1H)-ones **151** [41].



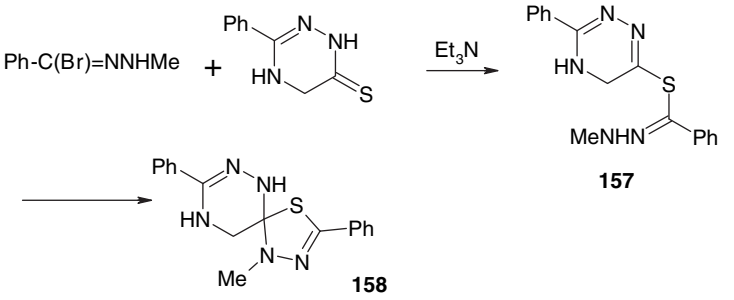
5.4.16 7H-1,2,4-Triazolo[3,4-*b*]-1,3,4-thiadiazines. Treatment of the thiohydrazonates **153** with acetic acid was reported recently to afford 7-arylhydrazono-7H-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **154** which proved to exist predominantly in the indicated hydrazone form [74, 75]. The tautomeric structures of the latter were elucidated by their spectral analyses and correlation of their acid dissociation constants with Hammett equation.



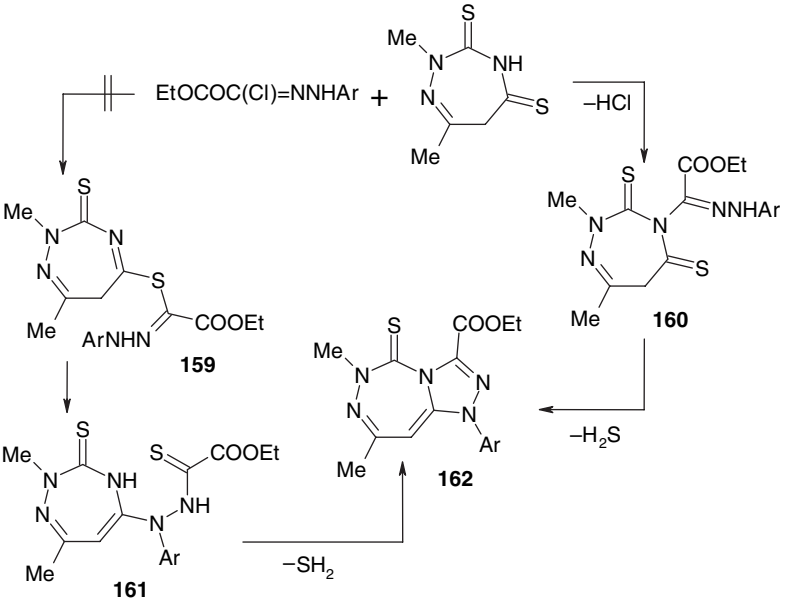
Similarly, 1,2-*bis*-(7H-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazin-3-yl)ethanes **156** were prepared by cyclization of the respective bis-thiohydrazonates **155** [117].



5.4.17 Spiro-1,3,4-thiadiazolo[2,6′][1,2,4]triazines. Reaction of N-methyl benzenecarbohydrazonoyl bromide with 3-phenyl-6-thioxo-1,4,5,6-tetrahydro-1,2,4-triazine in the presence of triethylamine gave the spirocycloadduct **158** [118]. The formation of the latter was considered *via* direct cycloaddition of nitrilime to the C=S bond or *via* cyclization of the initially formed thiohydrazonate **157**.

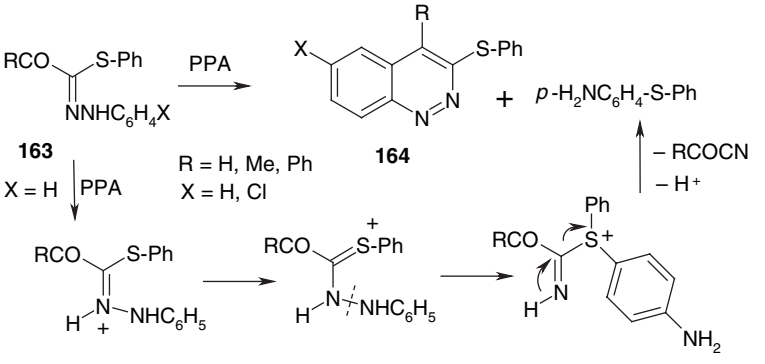


5.4.18 1,2,4-Triazolo[4,3-*d*]-1,2,4-triazepines. The reaction of ethyl (N-arylhydrazono) chloroacetate with 1,2,4-triazepine-3,5-dithione was reported to give 1,2,4-triazolo[4,3-*d*]-1,2,4-triazepines **162** directly. It was assumed that the latter product was produced *via* cyclization of the initially formed amidrazone derivative **160**. [119]. Further evidence is needed to substantiate that assumption as the product **160** can also result *via* the initial formation of hydrazonothioate **159** followed by tandem rearrangement into **161**



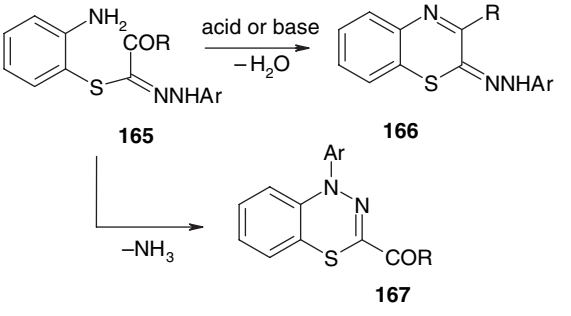
and cyclization of the latter to give **160**.

5.4.19 Cinnolines. Treatment of thiohydrazonates **163** with polyphosphoric acid was reported to yield 3-(arylthio)cinnolines **164** and phenyl 4-aminophenyl sulfide [14, 76]. The latter sulfide was considered to be formed through 3,5-sigmatropic rearrangement.

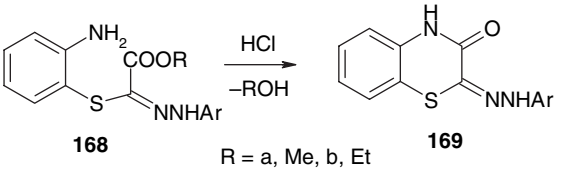


5.4.20 2H-1,4-Benzothiazines. An elegant method for synthesizing 2H-1,4-benzothiazine derivatives **166** is cyclization of the respective thiohydrazonates **165**, prepared from 2-aminothiophenols and α-ketohydrazonoyl halides. The cyclization is usually accomplished by treatment of these esters **165** with bases such as triethylamine or sodium ethoxide in ethanol [19, 120] or in some cases with hydrochloric acid in ethanol [121, 122].

In contrast to the foregoing results, it was indicated in one report [15] that the thiohydrazonates **165** from the reaction of α-ketohydrazonoyl chlorides and 2-aminothiophenol in refluxing dimethylformamide in the presence of triethylamine afforded 3-substituted-1H-4,1,2-benzothiadiazine **167** *via* elimination of ammonia [15]. This latter finding seems ambiguous as it involves nucleophilic displacement of amino group from an aromatic amine residue.

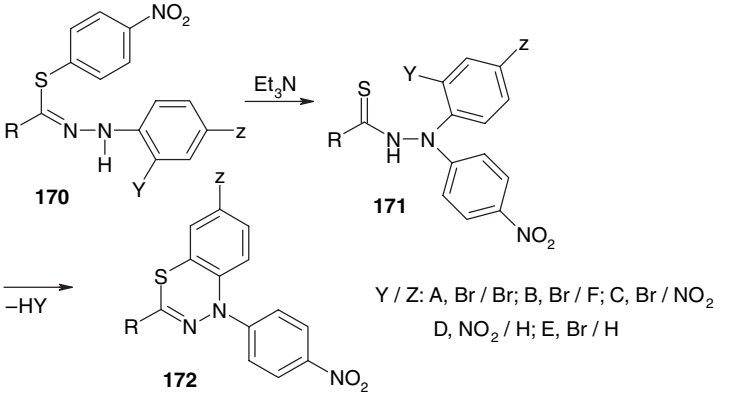


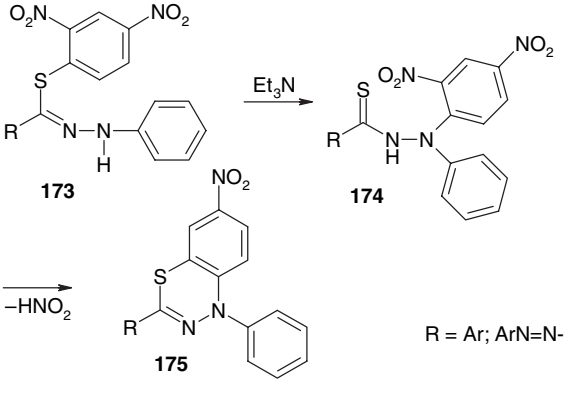
Treatment of the thiohydrazonates **168** with hydrochloric acid resulted in their cyclization to one and the same product namely the benzothiazin-3-one derivatives **169** [8, 19, 123].



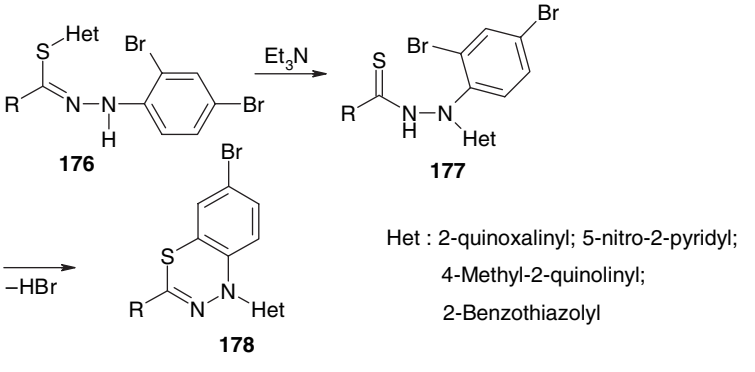
5.4.21 1H-4,1,2-Benzothiadiazines. When each of the 4-nitrophenyl N-(2,4-dihalophenyl)hydrazonothioates **170A,B** [23], N-(2-bromo-4-nitrophenyl) analogs **170C** [21] and 2-nitrophenyl analog **170D** [124] was refluxed in ethanol in the presence of triethylamine, the respective benzothiadiazine derivatives **172** were produced. Similar treatement of

2,4-dinitrophenyl N-phenylthiohydrazonates **173** gave also the respective benzothiadiazine derivative **175** [61]. These reactions were reported to proceed *via* tandem Smiles rearrangement of **170** and **173** to the respective thiohydrazides **171** and **174** which cyclized *in situ* to give the corresponding benzothiadiazines **172** and **175** as end products. This was confirmed by the fact that similar treatment of nonactivated 4-nitrophenyl N-(2-bromophenyl)benzenethiocarbohydrazonate led to only the respective thiohydrazide **171E** [23].

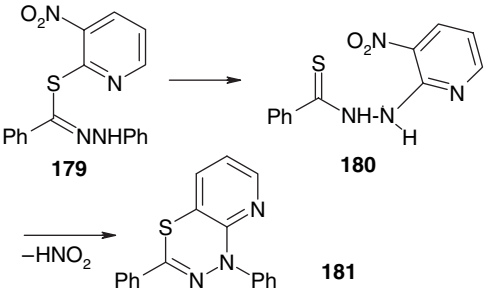




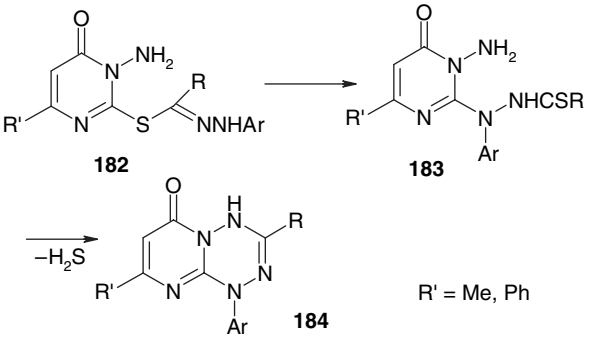
1-Heteroaryl-6-bromo-3-phenyl-1H-4,1,2-benzothiadiazines **178** were also obtained upon refluxing the respective heteroaryl thiohydrazonates **176** in ethanol in presence of triethylamine [23].



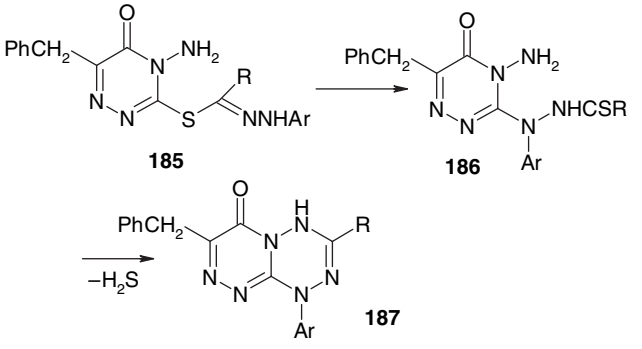
5.4.22 4H-Pyrido[3,2-*e*]-1,3,4-thiadiazines. An example of the title ring system **181** was prepared from the thiohydrazonate **179**, obtained from treatment of N-phenyl benzoicthiohydrazide with 2-chloro-3-nitropyridine in refluxing acetonitrile in presence of triethylamine. To account for the formation of the product **181**, it was assumed that the thiohydrazonate **179**, formed in the first step, underwent tandem *in situ* Smiles rearrangement to give **180** which in turn cyclizes *via* elimination of the elements of nitrous acid to afford 2,4-diphenyl-4H-pyrido[3,2-*e*]-1,3,4-thiadiazine **181** [61].



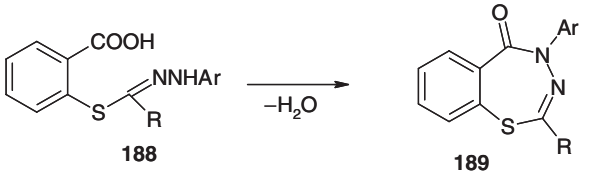
5.4.23 4H-Pyrimido[1,2-*b*]-1,2,4,5-tetrazines. Recently, it was reported that reaction of the hydrazonoyl halides with 3-amino-2-mercapto-6-methyl-4(3H)-pyrimidinone in boiling ethanol in presence of triethylamine, furnished pyrimido[1,2-b]-1,2,4,5-tetrazines **184**. The formation of the latter follows two steps namely (i) Smiles rearrangement of the initially formed thiohydrazonates **182** to yield the thiohydrazides **183** and (ii) cyclization of the latter to give 1,3,8-trisubstituted 4H-pyrimido[1,2-*b*]-1,2,4,5-tetrazines **184** as end products [40, 125].



5.4.24 1,2,4-Triazino[4,3-*b*]-1,2,4,5-tetrazines. Synthesis of the title compounds **187** was carried out by reaction of the hydrazonoyl halides with 4-amino-3-mercapto-6-benzyl-5(4H)-1,3,4-triazinone in boiling ethanol in presence of triethylamine. In this case, it seems the reaction furnished initially the thiohydrazonates **185** which underwent in subsequent steps rearrangement and cyclization to afford 1,2,4-triazino[4,3-*b*]-1,2,4,5-tetrazine derivatives **187** [126].

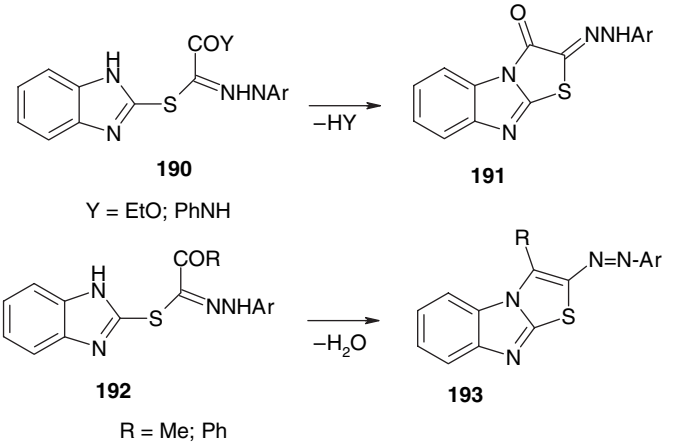


5.4.25 Benzo[e]-4,1,2-thiadiazepines. Base-catalyzed intramolecular condensation of S-(2-carboxyphenyl) thiohydrazonates **188** yielded benzo[e]-4,1,2-thiadiazepine derivatives **189** when refluxed in ethanol in the presence of triethylamine or sodium ethoxide [15].



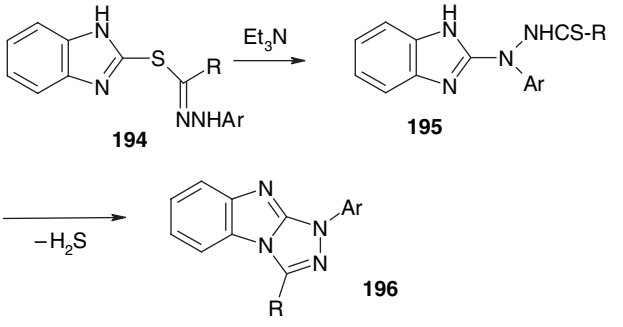
R = EtOCO; PhNHCO

5.4.26 Thiazolo[3,2-*a*]benzimidazoles. Thiohydrazonates **190**, prepared by reaction of the respective hydrazonoyl chlorides with 2-mercaptobenzimidazole, cyclized *in situ* to yield 2-arylhydrazono-3-oxothiazolo[3,2-*a*]benzimidazole **191** when treated with catalytic triethylamine in ethanol [33]. Use of 2-ketohydrazonoyl halides in this reaction under the same conditions yielded the respective 3-substituted-2-arylazothiazolo[3,2-*a*]benzimidazoles **193** [33, 99, 127].

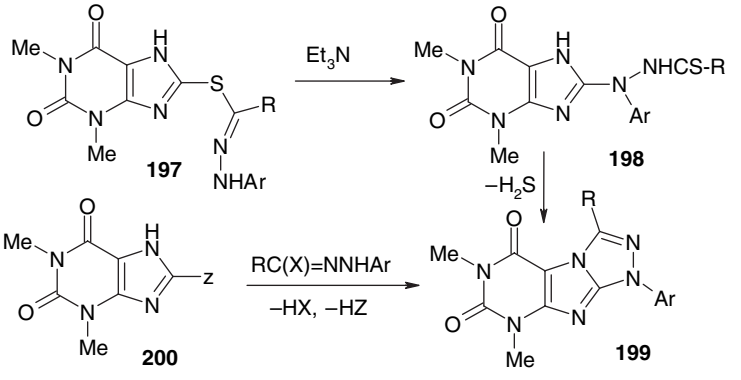


R = Me; Ph

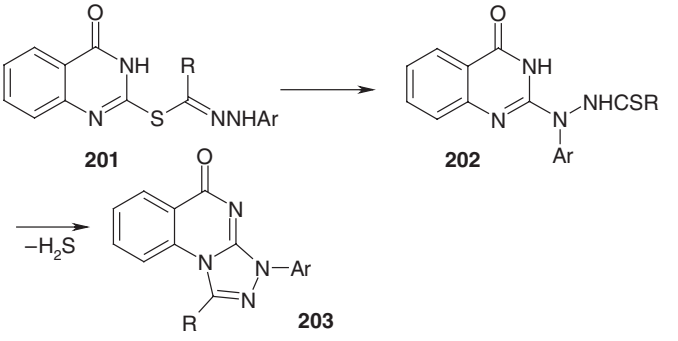
5.4.27 1,2,4-Triazolo[4,3-*a*]benzimidazoles. Thiohydrazonates **194**, derived from reaction of hydrazonoyl halides with benzimidazole-2-thione were reported to undergo Smiles rearrangement upon treatment with triethylamine to give the thiohydrazides **195** which cyclized *via* elimination of hydrogen sulfide to afford the title compounds **196** as end products [108].



5.4.28 1,2,4-Triazolo[3,4-*f*]purines. Thiohydrazonates **197**, prepared by reaction of 8-mercaptotheophylline and hydrazonoyl halides in dioxane in the presence of triethylamine, were reported to give 1,2,4-triazol[3,4-*f*]theophyllines **199** *via* rearrangement followed by elimination of hydrogen sulfide [128]. The structures of the latter products were confirmed by alternate synthesis by reaction of hydrazonoyl halides with either 8-methylthio-, 8-chloro- or 8-nitro-theophyllines **200** under the same reaction conditions.

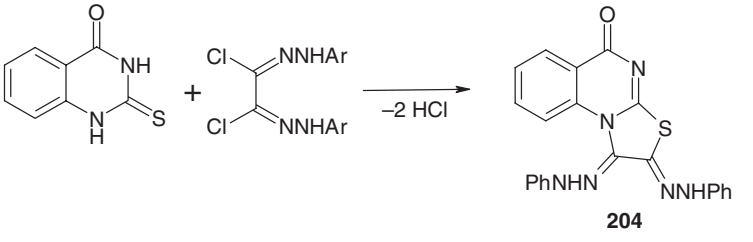


5.4.29 1,2,4-Triazolo[4,3-*a*]quinazolines. The thiohydrazonates **201**, prepared by reaction of various hydrazonoyl halides with 2-mercapto-4(3H)-quinazolinone, underwent *in situ* tandem Smiles rearrangement and cyclocondensation to yield 1,2,4-triazolo[4,3-*a*]quinazolin-5-ones **203** as end products [129].

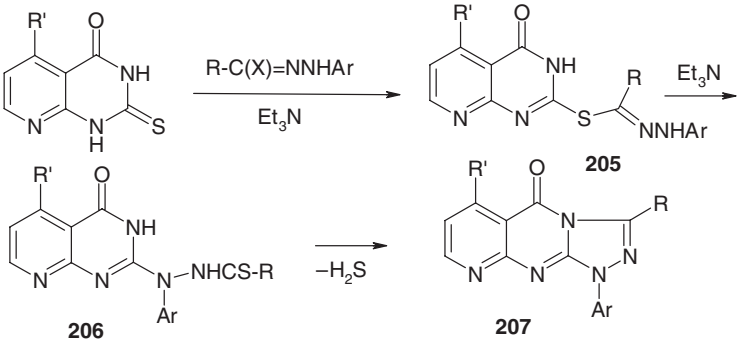


R = Me; Et; Ph; PhCH=CH; 2-thienyl; MeCO; EtOCO; PhNHCO; 2-thienoyl; 2-naphthoyl; 2-furyl; benzoyl

Recently, it was reported that reaction of quinazoline-2-thione with bis-(hydrazonoyl chloride) yielded bis-(phenylhydrazono)-thiazoloquinazoline derivative **204** [130].

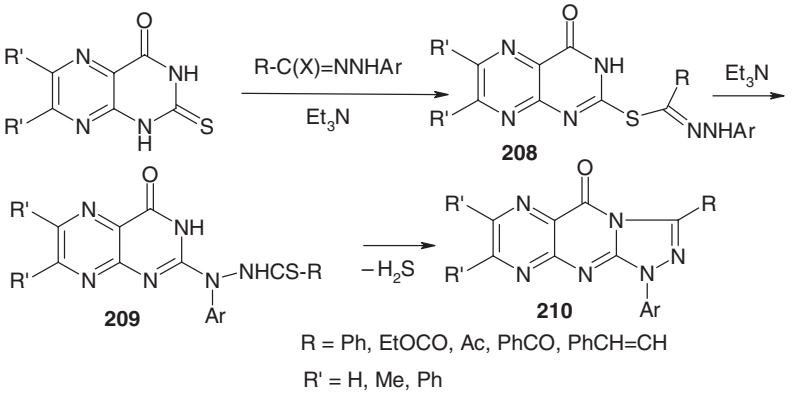


5.4.30 Pyrido[3,2-*e*][1,2,4]triazolo[3,4-*b*]pyrimidines. Reaction of hydrazonoyl halides with pyrido[3,2-*d*]pyrimidin-2-thione in boiling chloroform in the presence of triethylamine gave the thiohydrazonates **205**. The latter underwent consecutive rearrangement and cyclization, to give the respective pyrido[3,2-*e*][1,2,4]triazolo[3,4-*b*]pyrimidin-5-ones **207** [131].

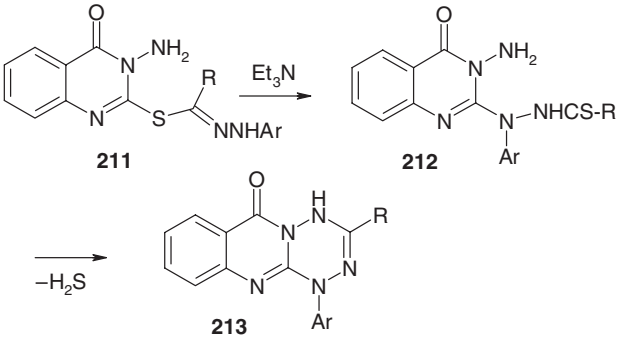


R = Ph, EtOCO R' = Ph, 2-thienyl

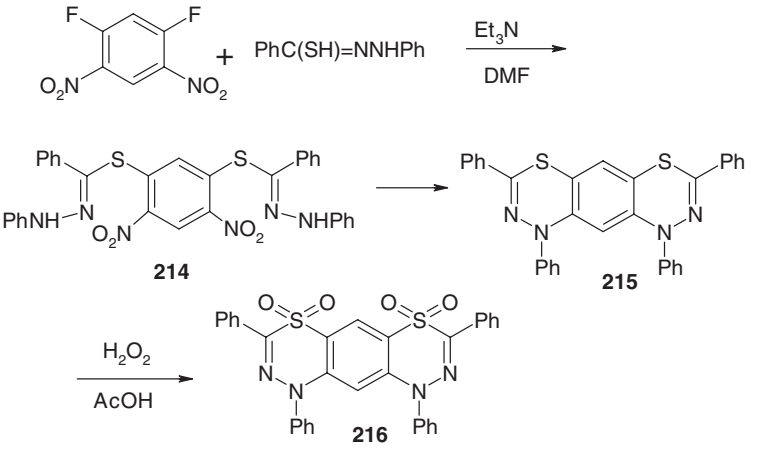
5.4.31 1,2,4-Triazolo[3,4-*b*]pteridines. Similarly, thiohydrazonate esters **208**, formed by reaction of hydrazonoyl halides with 1,3-dihydro-4-oxo-1,4-diazino[3,2-*d*]primidine-2-thione derivatives in boiling tetrahydrofuran in the presence of triethylamine, underwent consecutive *in situ* rearrangement and cyclization, to give the respective 1,2,4-triazolo[3,4-*b*]pteridin-9-ones **210** [132].



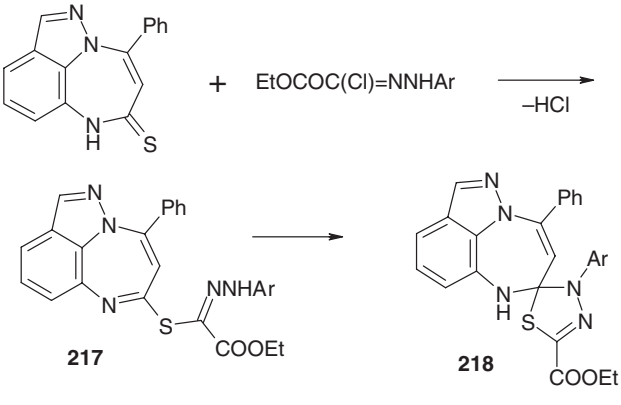
5.4.32 6H-1,2,4,5-Tetrazino[6,1-*b*]quinazolines. Reaction of 3-amino-2-mercapto-4(1H)-quinazolinone with hydrazonoyl halides in ethanol in the presence of triethylamine afforded the thiohydrazonates **211** which underwent tandem Smiles rearrangement and cyclocondensation [133] to give the respective 1,2,4,5-tetrazino[6,1-*b*]quinazolin-6-one derivatives **213**.



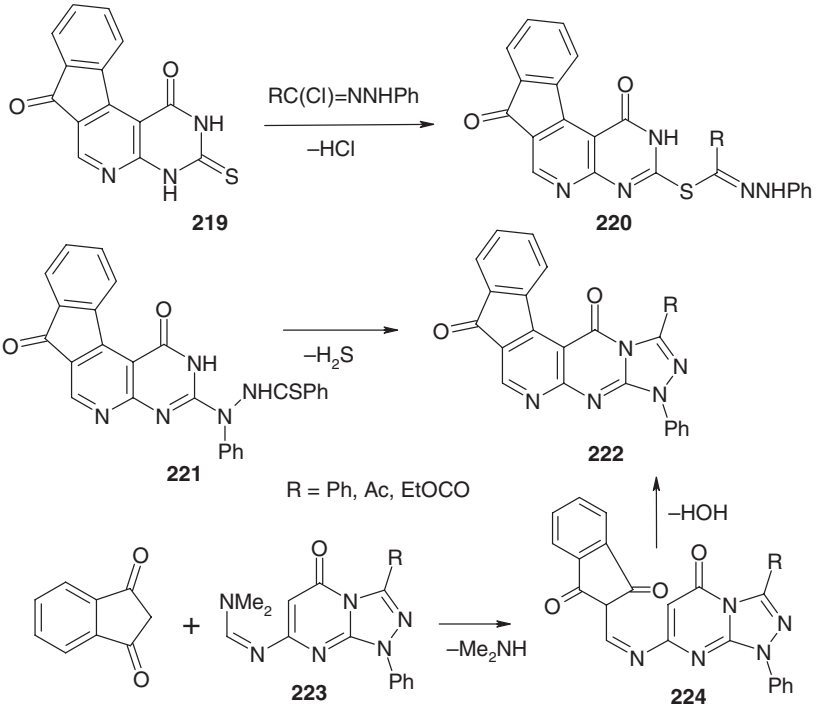
5.4.33 1H,7H-Benzo[1,2-*e*:5,4-*e*′]-bis[1,3,4]thiadiazines. Condensation of 1,5-difluoro-2,4-dinitrobenzene with N′-phenylbenzothio-hydrazide in dimethyl-formamide in the presence of triethylamine was reported to give **215** *via* cyclization of the initially formed thiohydrazonate **214** [61]. Oxidation of **215** with hydrogen peroxide in acetic acid yielded **216** [61].



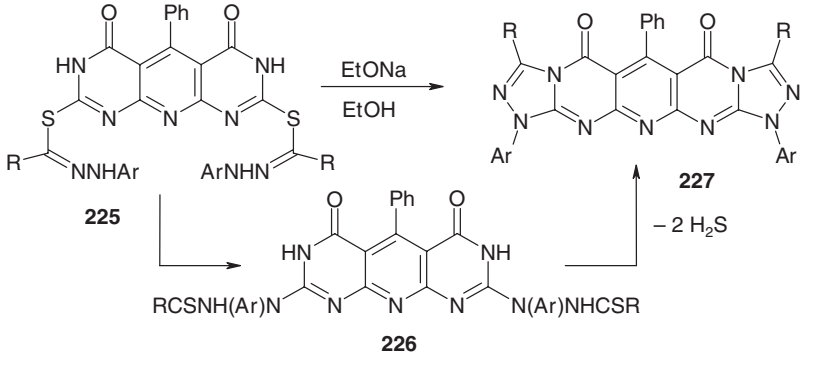
5.4.34 Spiro-1,3,4-thiadiazolo[2,6′]pyrazolo[1,5,4-*ef*][1,5]benzo-diazepines. Reaction of pyrazolo[1,5,4-*ef*][1.5]benzodiazepine-6-thione with ethyl (N-arylhydrazono)chloroacetate yielded the respective hydrazonothioate which cyclizes to give the spiro-1,3,4-thiadiazolo[2,6′]pyrazolo[1,5,4-*ef*][1,5]benzo-diazepines **218** [134].



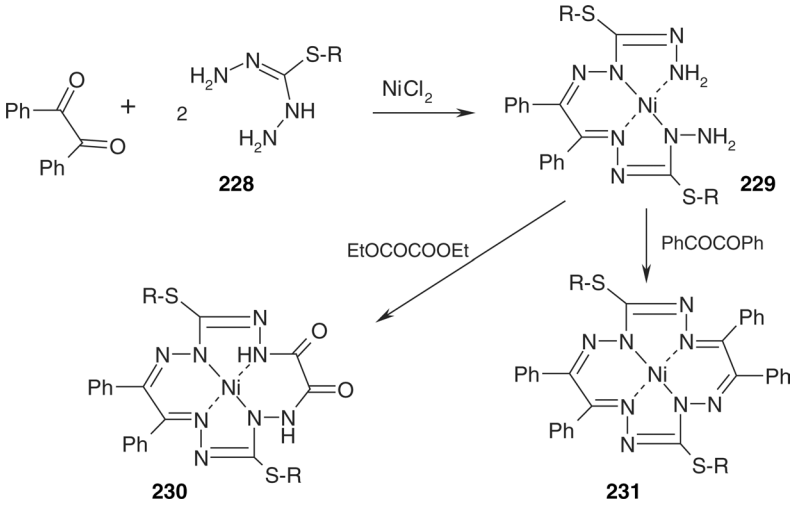
5.4.35 Indeno[2,3-*i*]pyrido[3,2-*e*][1,2,4]triazolo[3,4-*b*]pyrimidines. Treatment of the thione **219** with hydrazonoyl halides in chloroform in the presence of triethylamine afforded the respective 1,3-disubstituted-1H,7H-**i**ndeno[2,3-*i*]pyrido[3,2-*e*][1,2,4]triazolo[3,4-*b*]-pyrimidine-7,12-diones **222** *via* tandem rearrangement and cyclization of the initially formed thiohydrazonate **220** [135]. The structure of the products **222** were confirmed by their alternate syntheses by heating the respective 1,2,4-triazolo[3,4-*b*]pyrimidin-5-ones **223** with 2H-indene-1,3-dione in boiling ethanol to give **224** followed by heating the latter intermediates in acetic acid [135].



5.4.36 Pyrido[3,2-*f*:5,6-*f′*]bis-[1,2,4]triazolo[3,4-*b*]pyrimidines. Recently, Shawali and coworkers [55] reported that treatment of the *bis*-thiohydrazonates **225** with sodium ethoxide in refluxing ethanol gave the respective pyrido[3,2-*f*:5,6-*f′*]bis-[1,2,4]triazolo[3,4-*b*]pyrimidine-5,7-dione derivatives **227** *via* tandem Smiles rearrrangement and cyclization of the resulting bis-thiohydrazide **226**.

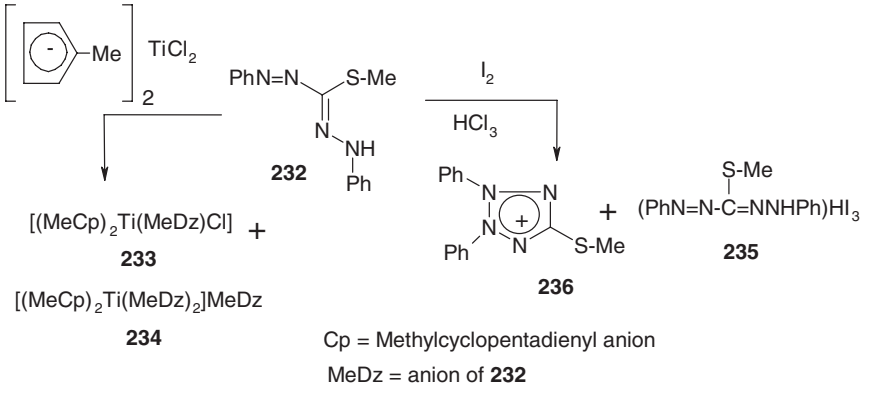


5.4.37 Miscellaneous reactions. Reaction of diphenylglyoxal and thiohydrazonate **228** in the presence of nickel chloride was reported to give the respective complex **229** [136]. Treatment of the latter with each of diethyl oxalate and diphenylglyoxal afforded the crown nickel complexes **230** and **231**, respectively [136].



Reaction of methyl N,2-diphenyldiazenecarbohydrazonothioate **232** with bis(methylcyclopentadienyl)titanium chloride yielded the two complexes **233** and **234** [137].

Treatment of methyl N,2-diphenyldiazenecarbohydrazonothioate **232** with iodine in chloroform gave the triiodide salt **235** and the chloroform solvate of the tetrazolium triiodide **236**. The structures of both salts were established by X-ray analysis [138].



6. Industrial and biological applications

Methyl and ethyl N-arylbenzenecarbohydrazonothioates were reported to be useful in the control of fungi that attack plants [50]. Also, ethyl N-(2,6-dichloro-4-trifluoromethylphenyl)-2,2-dimethylpropanehydrazonothioates demonstrated to be acaricidal and insecticidal agent which demonstrated 100% control of spodoptera eridania at 10 ppm [139–141].

1,3,4-Oxadiaol-2-yl thiohydrazonates were reported to show no *in vitro* antibacterial activity [142]. Some aryl N,2-diphenyldiazene-carbohydrazono-thioates were reported to be effective atimulators of flax and hem germination [143].

Hydrazonoyl thiohydrazonothioates of type $R^2-C(S-Z)=NNR^3R^4$, where $Z = -C(R^1)=NNR^5R^6$ and R^{1-6} = H, unsubsbtituted alkyl, aralkyl, heterocyclyl, proved to be good photoconductors and useful as electrophoto receptors [144].

Several alkyl N,2-diaryldiazenecarbohydrazonothioates were used in chemical analysis. For example, long chain alkyl N,2-diphenyldiazene-carbohydrazonothioates were used as carriers in simultaneous determination of o-nitrophenol and p-nitrophenol [145, 146]. Also, some other alkyl diazenecarbohydrazonothioates were used as chelating agents for the determination of Au, Pt and Pd in industrial waste water [147]. Allyl diazenecarbohydrazonothioate [148] was recommended as a regent for determination of Ir and Rh [149]

7. Conclusion

From the foregoing survey of thiohydrazonates, it can be seen that the main emphasis has lain in synthetic work, both in their preparation and their use as precursors or intermediates for synthesis of various heterocyclic compounds. The subject is ongoing and undoubtedly many further examples of both synthesis and reactions will become available as the chemistry of thiohydrazonates continues to develop. There remain, however, large areas of the chemistry of such esters, particularly regarding their physical properties, which have not been explored hitherto and could well repay the attention of some interested research groups.

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